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EXAMINER				
STOICA, ELLY GERALD				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/658,834

Applicant(s)

GANTIER ET AL.

Examiner

ELLY-GERALD STOICA

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) 8, 9, 46-74, 140, 142-144 and 306 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 5-7, 16-19, 21-23, 40, 43, 44, 139, 141, 279, 307, 308, 315, 316 and 332-347 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-946)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 10/04/2007.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

Continuation of Disposition of Claims: Claims pending in the application are 1,5-9,16-19,21-23,40,43,44,46-74,139-144,279,306-308,315,316 and 332-347.

DETAILED ACTION

Election/Restrictions

1. The remarks regarding Election/ restriction requirement in the amendment filed 10/09/2007 are noted. Applicant's traverse was noted and addressed in the previous Office action. With regard to the designation of the claim 279 as withdrawn, the Examiner acknowledges the inadvertent mistake and is considering the claim, as drawn to the Seq. Id. No.: 87, which is the elected specie (equivalent to the mutation E41Q in Seq. Id. No.:1). However, with respect to applicants' traversal of the restriction requirement, such traversal is not timely, the restriction having been made final in the previous Office Action. Applicant is advised of their right to petition the requirement if they deem such necessary.

Status of the claims

2. Claims 1, 5-9, 16-19, 21-23, 40, 43, 44, 46-74, 139-144, 279, 306-308, 315, 316 and 332-347 are pending in the application. Claims 8, 9, 46-74, 140, 142-144 and 306 are withdrawn from consideration as being drawn to non-elected subject matter, are retained for possible rejoinder upon allowance of a generic/linking claim. Claims 6, 7, 307, 341,342 and 344 were amended, claim 138 was cancelled, and claims 346 and 347 were added. Claims 1, 5-7, 16-19, 21-23, 40, 43, 44, 139, 141, 279, 307-308, 315, 316 and 332-347 are currently being examined.

Claim Objections

3. Claims 5-7, 23, 43, 279, 307-308, 341, 342, 344, 346, 347 and their dependent claims are objected to because of the following informalities: They contain non-elected subject matter, there being no allowable generic claim. Appropriate correction is required.
4. Claim 340 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.
5. Claim 347 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim(s) in independent form.

Declaration under 37 C.F.R. §1.132 of Dr. Manuel Vega

6. The executed declaration under 37 C.F.R. §1.132 of Dr. Manuel Vega, filed on 10/09/2007, was considered. The declaration presents facts that indicate that the mutant E41Q of the IFN α 2b has increased protease resistance, in vitro and in vivo, anti-proliferative and anti viral activity, with respect to the IFN α 2b which does not possess this modification. The declaration was not necessitated by any rejection made by the Office.

Withdrawn claim rejections

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The rejection of claims 1,5, 6, 16, 18, 19; 21-22, 43, 44, 307, 308, 315-316, and 332-339 under 35 USC § 101 is withdrawn in view of the amendment of claim 1.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 6, 17, 279, 341 and 347 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. In claim 1 it is unclear if the wording "one or two replacements" could mean an unlimited number of substitutions so that the essential motifs and regions that define the IFN alpha are no longer present. Hence, the meets and bounds of the claim could not be determined.

Claim 6 is indefinite because is not clear if the "one or more mutations mentioned in claim 1 are the mutations selected from the list in claim 6 or a totally new set of mutations.

Claim 7 is indefinite because it is not clear what the meaning of "human" is; i.e., if only

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the mutations indicated in claim 6 are made, the cytokine no longer possesses the amino acid sequence of the human IFN alpha 2b such that it could very well be that it resembles the Seq. Id of a non-human IFN alpha 2b. Further, it is not clear whether "human" means 'obtained from a human', which would exclude species not found in nature, or alternatively 'binds to human IFN alpha receptor', regardless of sequence.

Claim 17 is indefinite because it is not clear what is the "replication" that is supposed to be measured by RT-qPCR referring to.

Claims 18, 315 and 339 are indefinite because it is unclear if the antiviral activity of the mutant is compared with the anti-proliferative activity of the unmodified cytokine or if the comparison is actually made between the respective ratios of antiviral/antiproliferative activities of the mutant and the unmodified cytokine.

Claim 279 is indefinite because the meets and bound of "an interferon alpha structural homolog" cannot be assessed.

It is unclear, for the claims 332-335, how the mutants can be less stable, since they have to have increased proteolysis resistance (that is to say that the increased proteolysis resistance would necessarily confer them the increased stability property.

Claim 341 is indefinite because it contains the language "comprising only" which would indicate a narrow limitation followed by a broader limitation. -

11. 347 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically it is unclear if the wording "one or two replacements" could mean an unlimited number of substitution so that the essential

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motifs and regions that define the IFN alpha are no longer present. Hence, the meets and bounds of the claim could not be determined.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 5, 16-18, 19, 21-22, 40, 43, 44, 139, 141, 332-340 and 343 remain rejected and 346 is rejected under 35 U.S.C. 102(b) as being anticipated by Testa et al. (U.S. Pat. 5,676,942, 10/14/1997).

Testa et al. teaches of mixture of natural human alpha interferon species and subunits, known as IFN- α 3a, obtained from human blood upon induction with a virus (Example 1 and 2). According to the alignment performed with the program CLUSTALW (and exemplified in the attached documents Clustalw2.pdf and IFNs2.pdf) the components of the mixture of Testa et al. could be construed as mutants or variants of IFN2b, given the high degree of identity of the amino acid residues between the IFN α 2b and the Interferon α variants described by Testa et al in the Table 11. Since the

claims contain the language "comprises one or more amino acid replacements" the compounds of Testa et al. are construed as to represent IFN α 2b variants. The specific components are presented in table 11 and the N- terminal and C terminal sequences are described in tables 10 and 12 respectively. The components of the mixture, designated by the peak # of the HPLC purification process, contain peaks 2-6 that harbor IFN α 2b variants containing the mutation M161, which, according to the claims and the specification of the instant application, confers the mutant increased resistance to proteolysis and all the biochemical and biological properties of the mutants claimed in the instant application. For instance, peak #3 (the first mutant has the M161 mutation) has an increased antiviral specific activity than peak #1.1 and 1.2 (which contain the IFN α -2b) (table 4 corresponding lines). Its specific antiviral activity, as measured by the RK-13 cells, is between 40-80 times higher than the corresponding activity for the peak # 1.1 or 1.2, while its antiproliferative activity (measured in Daudi cells in the presence of the cytokine) is 1.6-2 times higher than the corresponding activity for the peak # 1.1 or 1.2 (Table 4). The mutant of peak # 3 contains, in addition to the M161 mutation, at least two more mutations located in the N terminus (T14A and R22G). By the description provided in the patent, any of the components of the IFN- α n3a mixture is intrinsically a structurally homolog of I IFN- α 2b and containing the mutations M161; meet the limitation of the instant claims. The mutant of peak #2 has an antiviral activity approximately 1.05 of the component of peak 1.1 or 1.2 while the antiproliferative activity is between 1.1-1.4 of that of the component of peak 1.1 or 1.2 and thus the limitations of claim 339 are met. By the nature of obtaining the mixture of

their invention, the mixture would have been exposed to serum or blood lysate, hence to proteolysis. The method of assessing the antiviral activity as in claim 17 of the application does not affect the properties of the mutant cytokine and therefore is not given patentable weight. Testa et al. also teach about the composition of his invention as a pharmaceutical composition (claim 1 of the patent) and possible formulated for oral administration (Col. 9, lines 24-35).

Therefore all the conditions and limitations of the claims 1, 5, 16-18, 19, 21-22, 43, 44, 139, 141, 332-340, 343 and 346 were anticipated by Testa et al.

On pages 31-34 Applicants argue that "none of the interferons described by Testa is an interferon α - 2a, -2b, or 2c and thus Testa et al. does not disclose a polypeptide that meets all limitations in the claims, and, thus, does not anticipate any of the claims." The arguments were carefully considered but not found persuasive because as per the actual way that the claims in the instant specification describe the invention, it may be construed that the compounds of Testa et al. represent IFN α 2b variants as presented supra.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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15. Claims 1, 6, 7, 23, 279, 307-308, 315, 316, 341, 342, and 344-347 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heinrichs et al. (WO 01/25438, 04/12/2001-cited by the Applicant) in view of Blank et al. (Eur. J. Biochem., 265, 11-19, 1999) and in further view of Jensen et al. (WO/01/36001, 05/25/2001) and Sheppard P. (U.S. Pat. 6,153,420).

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 7 is drawn to a human mutant interferon α -2b comprising the E41Q amino acid replacement in its sequence of amino acids, whereby the mutant exhibits increased resistance to proteolysis compared to the unmodified interferon alpha cytokine that does not comprise the one or more amino acid replacements. Claim 23 is drawn to a human mutant interferon α -2b comprising the E41Q amino acid replacement in its sequence of amino acids (that is Seq. Id. No: 87), whereby the mutant exhibits increased resistance to proteolysis and further comprises the mutation R23K (claim 23). Claims 279 The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The claims are drawn isolated interferon alpha comprising one or more amino acid replacements in its sequence of amino acids, whereby the interferon alpha cytokine exhibits increased resistance to proteolysis compared to the unmodified interferon alpha cytokine that does not comprise the one or more amino acid replacements. The interferon is interferon α -2b, and more specifically a human mutant interferon α -2b comprising the E41Q amino acid replacement in its sequence of amino acids, whereby the mutant exhibits increased resistance to proteolysis compared to the unmodified interferon alpha cytokine that does not comprise the one or more amino acid replacements. Claim 23 is drawn to a human mutant interferon α -2b comprising the E41Q amino acid replacement in its sequence of amino acids (that is Seq. Id. No: 87), whereby the mutant exhibits increased resistance to proteolysis and further comprises the mutation R23K (claim 23). Claims 341-342 and 343-344 are drawn to mutants corresponding essentially to the Seq. Id. No: 87.

As presented in the previous Office action, Heinrichs et al teach novel interferon-alpha homologue polypeptides. The mutants of the invention possess clinical utility in that they are designed towards optimization for use as pharmaceuticals and to overcome dose-limiting toxicity, receptor cross-reactivity, and short serum half-lives significantly reduce the clinical utility of many of these cytokines. The existence of abundant naturally occurring sequence diversity within the interferon-alphas (and hence a large sequence space of recombinants) along with the intricacy of interferon-

alpha/receptor interactions and variety of therapeutic and prophylactic activities creates an opportunity for the construction of superior interferon homologues (p. 2-3). Heinrichs et al. do not specifically teach the mutation E41Q or the R23K.

Blank et al. teach possible cleavage sites for the IFN a-2b molecule (Fig. 5), which include the E41 residue, which, contrary to Applicants assertion in the remarks on page 39, is a cleavable site for Glu-C protease, as indicated by the boxed residues). The R23K mutation is found naturally in IFN a-2a as indicated in Seq. Id. No: 182.

Jensen et al. teach the introduction of E38N glycosylation site in IFN γ , to obtain a protease resistant mutant for a position of the residues, which exposed at least 50% to the surface of the polypeptide (p. 16, line 32 to p.17, line 2). Such an exposed residue would constitute a potential cleavage site for proteases like Glu-C, as taught by Blank et al.

Sheppard teaches a novel serine protease homologous to glutamyl endopeptidases which are found in tissues exposed to the external environment, like small intestine and colon (col. 5, line 21 to col. 6, line 31). This teaching is especially relevant for claim 343, which discloses a pharmaceutical composition of the mutant interferon that is formulated for oral use. Once in the digestive system, the active compound (mutant interferon) would necessarily have to cross the small intestine and colon and be exposed to proteases as taught by Sheppard.

It would have been obvious for a person of ordinary skill in the art at the time that the invention was made to use the methods of Heinrichs to mutate the interferon a-2b at E41 to confer the mutant increased resistance to Glu-C protease with a reasonable

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expectation of success. The motivation to do so would have been suggested by Heinrichs et al namely to improve the serum half-life and stability. Further combination of the teachings of Heinrichs et al. and Blank et al. with the teachings of Jensen et al. would have assured that the mutant thus obtained is resistant to proteases like the ones described by Sheppard especially if the Interferon mutant is formulated for oral use and resistance against Glu-C endopeptidases would be essential.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1, 5-7, 16-19, 21-23, 40, 43, 44, 139, 141, 279, 307-308, 315, 316 and 332-347 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 68-70, 72-79, 81-82 84-86, 89-90 of

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copending Application No. 11/176830. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to proteolytic resistant Interferon variants or compositions containing the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/
Primary Examiner, Art Unit 1647